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Effects of Neonatal Tactile Stimulation and Maternal Separation on the Anxiety and the Emotional Memory in Adult Female Rats

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Abstract: We investigated the long-lasting effects of early postnatal tactile stimulation (TS) and maternal separation (MS) on the emotional behaviors of adult female rats. A split-litter design was introduced to remove confusing factors such as maternal disturbance. Pups of the non-tactile stimulation (NTS) group did not receive any handling. Pups subjected to the TS treatment were handled and marked for approximately 30 s daily from postnatal days (PND) 2 – 9 or from PND 10 – 17. Pups subjected to the MS treatment were handled and marked in the same way as the TS pups and then individually placed in a cup with familiar nest bedding for 1 h daily. At the age of 3 months, female rats with different neonatal experiences were employed in the light/dark box test and the one-trial passive avoidance response. Both PND 2 – 9 TS and PND 10 – 17 TS groups exhibited more time spent in the illuminated chamber of the light/dark box, and longer step-through latencies in the passive avoidance response when compared to the NTS group, indicating that early life TS treatment reduced novelty-induced anxious emotion and facilitated the retention of emotional memory in adult female rats. No significant effects were found on any behavioral measures between the MS groups and the TS groups, suggesting that neonatal short-time MS treatment was not intensive enough to alter the emotional behaviors, at least in female rats. Infantile age was not an effective factor for these measures. This result supports the hypothesis that neonatal tactile stimulation and maternal separation lead to different effects on the neural development of postnatal pups.

Key words: Rat; Tactile stimulation; Maternal separation; Anxiety; Emotional memory; Neonatal period

新生期触觉刺激和母婴分离对雌性大鼠成年后的焦虑和情绪记忆的影响

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摘要: 采用 split-litter 法对仔鼠进行分组和处理, 共 5 组: NTS 组(未经实验人员抓握和标记), PND 2—9 TS 组和 PND 10—17 TS 组(分别在仔鼠出生后的 2—9 天、10—17 天, 每天短暂抓握和标记仔鼠), PND 2—9 MS 组和 PND 10—17 MS 组(分别在仔鼠出生后的 2—9 天、10—17 天, 除了按 TS 组相同方式抓握并在不同部位标记外, 每天把仔鼠与母鼠分离 1 h)。待雌鼠成年后, 进行明/暗箱测试和一次性被动回避反应测试。结果发现: 与 NTS 组相比, PND 2—9 TS 组和 PND 10—17 TS 组的雌鼠在明/暗箱测试中停留于明室的累计时间明显较长, 在被动回避作业中的重测试潜伏期也明显较长, 表明新生期的触觉刺激经历减少雌性大鼠成年后在新异环境中的焦虑, 并改善情绪记忆。与相应 TS 组相比, MS 处理组的所有行为指标都无显著性差异, 说明短时间母婴分离对雌鼠成年后的焦虑和情绪记忆无明显影响。结果提示, 新生期的触觉刺激和母婴分离经历对仔鼠神经系统的发育产生不同的长期效应。

关键词: 大鼠; 触觉刺激; 母婴分离; 焦虑; 情绪记忆; 新生期

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It has been widely shown that environmental stimuli during the early postnatal weeks (weeks 2－3) produce long-lasting effects on neural and behavioral development in rodents (Anisman et al, 1998; Fernández-Teruel et al, 2002). For example, adult rats that experience early handling treatment, in which neonatal pups are removed from the nest and held gently for 10－15 min daily, exhibit less anxiety (Levine et al, 1967; Fernández-Teruel et al, 1990, 1991; Ferre et al, 1995) and better cognitive performance (Lehmann et al, 2002; Meaney et al, 1988; Núñez et al, 1995) when compared to non-handled controls. The early handling procedure involves four factors: alteration of the mother-infant relationship, novelty exposure, tactile stimulation (TS), and maternal separation (MS) (Tang, 2001). It was reported that mothers of handled pups showed more frequency of care-taking behaviors (i.e., licking and grooming, arched-back nursing) than mothers of non-handled pups (Liu et al, 1997). Adult offspring of mothers with higher care-taking behaviors exhibited less anxiety and better performance in the Morris water maze (Liu et al, 1997, 2000; Caldji et al, 1998). Recently, it was reported that neonatal exposure to novelty for 3 min daily also facilitated hippocampal-dependent memory and synaptic plasticity (Tang, 2001; Tang & Zou, 2002; Zou et al, 2001). However, the roles of the other two important factors, TS and MS, have not yet been studied sufficiently and it is possible that they may influence the neural development of postnatal pups in different ways.

In the present study, we investigated the long-term effects of early life repeated TS and MS on the anxiety and the emotional memory in adult female rats, by using the light/dark box test (the L/D test) and the one-trial passive avoidance response (PAR). It was reported previously that early handling led to less anxiety and better emotional memory in adult female rats (Ferré et al, 1995; Gschanes et al, 1998). In order to remove confounding factors (e.g. maternal disturbance, novelty exposure), and to verify more specific roles of early life TS and MS treatments, we made some modifications from the classic early handling paradigm, such as a split-litter design (Tang, 2001), and familiar olfactory and auditory cues when pups were manipulated.

1　Materials and Methods

1.1　Subjects

Wistar rats were obtained from Kunming General Hospital and bred in our laboratory colony. Female rats at the age of 3－4 months were mated with breeder males (3∶1 or 2∶1) and housed individually after pregnancy. Female offspring served as the subjects in this study and were housed with male siblings and their mothers until weaning. Male siblings were assigned to another experiment. Food and water were available *ad libitum*. The colony room was maintained at 22 ± 1 ℃ in a 12 h light/dark cycle (light on: 7:00－19:00). All experiments were conducted during the light phase. The order of neonatal manipulation and adult testing was counterbalanced between different groups.

1.2　Tactile stimulation (TS) and maternal separation (MS)

The pup birth day was defined as postnatal day 0 (PND 0). The number of pups in each litter was culled to 9－12 with an effort to balance the ratio of sex. We used a split-litter design to divide pups into five groups: the non-tactile stimulation (NTS) group, the PND 2－9 TS group, the PND 10－17 TS group, the PND 2－9 MS group, and the PND 10－17 MS group. In this study nine litters were used. Each group possessed nine pups. The TS and MS manipulations were conducted between 9:00 and 13:00 once daily from PND 2 through PND 9, or from PND 10 through PND 17. At first, the mother of each litter was removed from the nest and put into an adjacent cage bedded with sawdust. The mother was returned to the nest after 3－4 min during which pups were handled and marked. Pups assigned to the TS groups were picked up individually and held gently by an experimenter in gloves with some odour of the nest. The pup's back or rear area was stained regularly with a brush dipped in dye-liquid (0.1% Picric acid) 10 times for approximately 30 s. The remnants of dye-liquid on the pup's skin was absorbed with soft paper and then the pup was placed back into the home cage. Pups allotted to the MS groups were also handled and marked in the same way as the TS pups but at the contralateral skin to distinguish from pups of other groups in the same nest, and then individually placed into a circular cup (11 cm diameter) bedded with sawdust taken from its own home cage. The cups were immediately put into an incubator (30 ± 0.5 ℃). After 1 h of separation, the pups were returned to their own nests. Since pups of the TS groups and the MS groups were matched with the same

extent of handling and mark, the TS groups were considered as the control of the MS groups. Pups assigned to the NTS group were left in the nests without any handling and served as the control of the TS groups.

On PND 22, mothers were taken away from their nests and 3 – 5 female siblings with different treatments were bred in one Plexiglas cage until behavioral testing. As the body weight is an indication of general nutritional development, all subjects were weighed at PND 30, 60, and 90.

1.3 Behavioural testing

1.3.1 Apparatus The testing apparatus was a step-through avoidance system (GEMINI Ⅱ, San Diego Instruments, USA) which comprised an illuminated chamber (a 50 watt bulb on the top) and a dark chamber. A guillotine door connected the two chambers. A personal computer controlled switching of the door, triggering of the scrambled electric foot-shock on the floor grid bars, and recording of the latency for rats to enter the dark side from the bright chamber. The L/D test and the one-trial PAR test were conducted in the same apparatus.

1.3.2 L/D test The L/D test is based on the innate fear of rodents to illuminated area and on the spontaneous exploration in response to novel environment (Bourin & Hascoët, 2003). On the first day of testing, adult female rats (PND 90 – 110) were placed individually into the bright chamber, facing away from the raised guillotine door. They were permitted to explore freely between the bright chamber and the dark chamber for 300 s. A 'true' entry was defined as the placement of all four paws into a chamber. An experimenter sitting in front of the apparatus recorded the time that the rat stayed in each chamber with a stopwatch. These data were classified as four parameters: the latency for the first enterance into the dark chamber, the latency for the first re-enterance into the bright chamber, the total time spent in the bright chamber, and the transitions between the two chambers.

1.3.3 One-trial PAR test On the second day, an acquisition trial was performed for each animal as reported elsewhere (Gschanes et al, 1998; Ribeiro et al, 1999). In short, each rat was put into the bright chamber, facing away from the raised door. When the rat entered into the dark chamber, the phototube beams were blocked and thus triggered the closure of the door and the delivery of an inescapable electric foot-shock (0.78 mA; 50 Hz; 3 s). After 3 – 5 s, the rat was taken away from the dark chamber and returned to its nest.

Twenty-four hours later, the retention of emotional memory was measured in the same manner as the acquisition trial except that no electric foot-shock was delivered. The step-through latency was measured up to a maximum of 300 s.

1.4 Data analyses

Body weight and PAR test data were analyzed using two-way [TS treatment (NTS, PND 2 – 9 TS, PND 10 – 17 TS) × litter] or three-way [MS treatment (TS, MS) × infantile age (PND 2 – 9, PND 10 – 17) × litter] analyses of variance (ANOVAs) with repeated measures. The data from the L/D tests was analyzed using two-way or three-way ANOVAs. When necessary, ANOVAs were followed by *post-hoc* Duncan tests. A paired t test was used to compare the latencies between the training trial and the test trial in the PAR test. Differences were considered significant if $P < 0.05$.

2 Results

2.1 Effects of neonatal experiences on the development of body weight

The body weight data at three developmental ages (PND 30, 60, 90) are shown in Tab.1. For the TS treatment and the MS treatment, a repeated-measure ANOVA revealed a significant effect of age ($F_{2,32} = 1\,484.0$, $F_{2,48} = 1\,599.8$, respectively; both $P < 0.000\,1$), litter ($F_{8,16} = 9.08$, $F_{8,24} = 12.2$, respectively; both $P < 0.000\,1$) and a significant interaction between age and litter ($F_{16,32} = 4.44$, $F_{16,48} = 5.42$, respectively; both $P < 0.000\,1$) on body weight. However, the main effects of the TS treatment ($F_{2,16} = 0.71$, $P = 0.5$), the MS treatment ($F_{1,24} = 0.77$, $P = 0.4$), infantile age ($F_{1,24} = 3.36$, $P = 0.10$), and their interactions with litter or age were not significant (all $P > 0.05$), suggesting that neonatal TS and MS treatments in this study did not affect the development of body weight.

2.2 Effects of neonatal experiences on the L/D test

Data from the L/D test are shown in Tab. 2. For the parameters of the latency of entering into the dark chamber, the latency of re-entering into the light chamber, and the transitions between two chambers, the TS treatment did not exhibit significant effects ($F_{2,16} = 2.18$, 0.46, 1.09; $P = 0.15$, 0.64, 0.36, respectively). However, for the total time spent in the bright chamber, there were significant main effects of the TS treatment ($F_{2,16} = 4.17$, $P < 0.05$) and litter ($F_{8,16} = 2.96$, $P < 0.05$). Duncan tests showed that the

Tab. 1　The effects of early life tactile stimulation and maternal separation on the development of body weight　(g)

Age	NTS	PND 2 – 9 TS	PND 10 – 17 TS	PND 2 – 9 MS	PND 10 – 17 MS
PND 30	55.6 ± 4.2	57.2 ± 3.3	56.4 ± 4.2	54.7 ± 5.1	56.7 ± 4.2
PND 60	130.8 ± 10.0	134.4 ± 10.6	131.9 ± 6.4	136.1 ± 12.0	127.1 ± 9.0
PND 90	219.7 ± 12.9	223.9 ± 13.3	222.2 ± 7.6	210.6 ± 15.9	218.6 ± 12.8

PND: postnatal day; NTS: the non-tactile stimulated group; TS: tactile simulation; MS: maternal separation. $n = 9$ per group. Mean ± *SE*.

Tab. 2　The effects of early life tactile stimulation and maternal separation on the light/dark box test

	NTS	PND 2 – 9 TS	PND 10 – 17 TS	PND 2 – 9 MS	PND 10 – 17 MS
Latency into dark chamber (s)	17.1 ± 2.5	23.2 ± 6.9	36.1 ± 8.6	24.0 ± 4.2	23.3 ± 4.5
Latency into light chamber (s)	72.5 ± 28.9	37.9 ± 6.7	66.0 ± 24.9	58.9 ± 20.6	35.6 ± 8.1
Total time in light chamber (s)	67.2 ± 10.4	99.9 ± 15.0*	104.2 ± 13.1*	87.0 ± 18.1	83.1 ± 11.6
Transitions	5.1 ± 0.7	6.3 ± 0.4	6.2 ± 0.7	6.2 ± 0.7	6.2 ± 0.8

* $P < 0.05$ *vs* the NTS group (Duncan test). $n = 9$ per group. Mean ± *SE*.

PND 2 – 9 TS group ($P < 0.05$) and the PND 10 – 17 TS group ($P < 0.05$) spent more time in the bright chamber than did the NTS group.

No significant effects of the MS treatment, the infantile age, and their interaction were found on any parameters of the L/D test (all $P > 0.10$), though the significant effect of litter appeared again for the total time spent in the bright chamber ($F_{8,24} = 4.18$, $P < 0.01$).

2.3　Effects of neonatal experiences on the one-trial PAR test

There were significant effects of the trial ($F_{1,16} = 56.6$, $P < 0.000\ 1$), the TS treatment ($F_{2,16} = 4.77$, $P < 0.05$), and the trial × treatment interaction ($F_{2,16} = 5.09$, $P < 0.05$) on the step-through latency (STL). In the training trial, there was no significant effect of the TS treatment ($F_{2,16} = 0.44$, $P = 0.6$). However, neonatal TS treatment significantly affected the STL in the test trial ($F_{2,16} = 4.94$, $P < 0.05$). Duncan tests showed that the PND 2 – 9 TS group exhibited much longer STL than that of the NTS group ($P < 0.01$). There was a tendency to significance when compared the PND 10 – 17 TS group with the NTS group ($P = 0.08$).

A repeated-measure ANOVA was also performed to reveal the effects of the MS treatment. A significant effect of the trial appeared again ($F_{1,24} = 108.6$, $P < 0.000\ 1$), but there were no obvious effects of the MS treatment ($F_{1,24} = 0.29$, $P = 0.6$), the infantile age ($F_{1,24} = 0.06$, $P = 0.8$) and the trial × treatment interaction ($F_{1,24} = 0.30$, $P = 0.6$).

All groups achieved longer STL in the test trial than in the training trial (all $P < 0.05$ or 0.01), suggesting that all groups acquired foot-shock information after the training trial (Fig. 1).

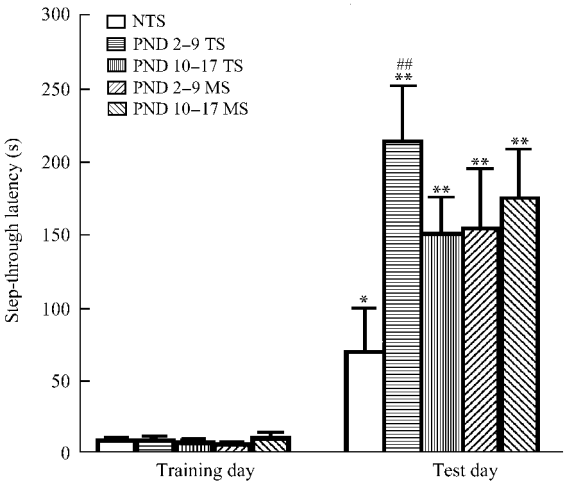

Fig. 1　The effects of early life tactile stimulation and maternal separation on the one-trial passive avoidance response

All groups achieved longer step-through latency in the test trial than in the training trial (*: $P < 0.05$; **: $P < 0.01$, paired t test). ##: $P < 0.01$ (Duncan test), *vs* the NTS group in the test trial. $n = 9$ per group. Mean ± *SE*.

3　Discussion

3.1　Why did we use the split-litter design?

There are two forms of experimental design to study the early handing paradigm: the between-litter design and the split-litter design. For the between-litter design, some litters in which pups and their mothers are left completely undisturbed serve as the non-handling group, and some other litters with handled pups serve as the handling group. In this way, several factors are introduced, including maternal disturbance, novelty exposure when pups are held, experimenter's tactile stimulation, and maternal separation, between the non-handling group and the handling group. One of these factors or the combination of several factors may contribute

to the beneficial effects of the early handling paradigm (Caldji et al, 1998; Liu et al, 1997, 2000; Meaney et al, 1988; Rodrigues et al, 2004; Tang, 2001). Therefore, by using the between-litter design, the findings that early handling led to less anxiety (Ferré et al, 1995) and improved emotional memory (Gschanes et al, 1998) in adult female rats could not only attribute to tactile stimulation but also other factors such as the mother-pup relationship or novelty exposure.

Recently, the split-litter design was used to investigate the long-term effects of neonatal novelty exposure on learning and memory in rats (Tang, 2001; Tang & Zou, 2002; Zou et al, 2001). In the split-litter design, all groups derived from the same litters and received maternal care from the same mothers. Specifically, the novelty-exposed pups and the control pups were matched in same extent of experimenter's handling. In this way, confounding factors including heredity, maternal disturbance, and experimenter's tactile stimulation were removed, and the effects of the neonatal novelty exposure were explored. Unfortunately, it was unclear whether the experimenter's tactile stimulation caused any effects. So, we used the split-litter design to explore whether a special way of handling with brushing actions on the skin of neonatal rat pups could lead to similar effects in female adult rats.

3.2 The long-term effects of neonatal tactile stimulation

We performed the L/D test and the one-trial PAR test in the step-through avoidance apparatus for two reasons: (1) the avoidance apparatus which consists of an illuminated and a dark compartment can be used as a L/D box; (2) all rats need to habituate to the apparatus before step-through training in order to reduce any neophobic response that may interfere with the testing in the PAR task, thus it is convenient to complete the habituation and the L/D test at the same time. This procedure has been adopted previously (Yamada et al, 2003).

In the L/D test, naïve rats spent approximately 60% – 80% of the total time to stay in the dark chamber, reflecting an aversive influence of the bright chamber on these rats in our study. Adult female rats treated with the repeated TS treatment during PND 2 – 9 or PND 10 – 17 spent significantly more time in the bright chamber compared to the NTS group. Bourin & Hascoët (2003) considered that the duration spent in the bright chamber was the most consistent and useful parameter for assessing anxiolytic-like actions of a compound, and Kazlauckas et al (2005) found that there was a significant positive correlation between this parameter and the exploratory behaviors in rats. Therefore, our finding suggested that neonatal tactile stimulation led to less anxiety and more persistent exploration in adult female rats. The reduced anxiety in the TS-treated rats could not be attributed to their locomotor ability since there was not significant difference for the transition numbers between different groups.

In the training trial of the PAR test, there was no significant effect of the TS treatment on the STL, suggesting that the reduced anxiety of the TS-treated rats in the L/D test did not necessarily mean longer STL before they encountered foot-shock in the dark chamber. After the foot-shock, all groups achieved longer STL in the test trial than in the training trial. Furthermore, the TS-treated rats had longer STL when compared to the NTS group, reflecting an improved retention of emotional memory for foot-shock information in the TS-treated rats. Therefore, the length of the STL in the test trial was related with the footshock experience, but not with the L/D test.

It was also unlikely to attribute the enhanced memory to the hypersensitivity of pain response, as it was reported previously that neonatal handling (D'Amore et al, 1991; Pieretti et al, 1991) and TS treatment (Stephan et al, 2002), which is similar to the TS treatment in our study, induced longer latencies in the tail flick and the hot plate tests (that is, hyposensitivity of pain response) in adulthood. The improved memory might reflect better dynamic processes such as consolidation, integration and organization in stimulated animals than in non-stimulated ones (Gschanes et al, 1998). The mechanisms underlying the improvement in the TS-treated rats need to be further explored.

3.3 The long-term effects of neonatal maternal separation

We did not find any statistically significant effects of PND 2 – 9 or PND 10 – 17 MS treatment on behavioral measures in this study. During the periods of the MS treatment, pups could detect familiar olfactory cues from their own nest bedding and auditory cues from the vocalizations of siblings. These familiar cues might make the MS-treated pups feel 'safe', blocking the elevation of stress response. It was proposed that differences in maternal separation procedure such as the length of pups' separation from the mothers, bedding

type, and environment temperature could be responsible for discrepant results (Kehoe et al, 1996; McCormick et al, 1998). The length of maternal separation is an important parameter, and obvious elevation of plasma corticosterone was observable if the duration extended for longer period (e.g. 3 h or more) (Boccia & Pedersen, 2001; Hall et al, 1999; Kalinichev et al, 2002a, b). However during this time other factors such as hunger might be involved.

3.4 Body weight and infant age

There were no discernible effects in terms of body weight during the various developmental stages between different groups, indicating that neonatal TS and MS treatment did not alter the overall nutrition or growth development. In addition, there were no significant effects of the infant age on any behavioral measures in this study, suggesting that neural development during the neonatal period might not be discernable to environmental stimuli on rat pups.

Our data demonstrated that early life tactile stimulation and maternal separation led to different long-term effects on the anxiety and the emotional memory, at least in female rats. Tactile stimulation caused a lower level of fearfulness to novelty exposure, and improved emotional memory in adulthood, suggesting that tactile stimulation may play a role in the early handling procedure. Our data also suggested that short-time (1h/d) maternal separation did not significantly modify the process of emotional response and memory retention. Future studies should examine whether there is a sexual difference and whether an alteration could be observable after a drug or environmental challenge to animals which have experienced maternal separation.

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本刊编委蔡景霞研究员简介

蔡景霞研究员

蔡景霞,女,研究员,博士生导师。1940 年出生于四川省绵阳市,1960 年毕业于云南大学生物系,同年分配到中科院昆明动物研究所工作至今。1984—1987 年被选送到美国耶鲁大学神经生物学系 P.S.Goldman-Rakic 教授研究室进修。现任云南省生理学会副理事长、中国神经科学学会理事、中国生理心理专业委员会常务委员、*Neuroscience Bulletin* 编委、中国老年学学会衰老与抗衰老科学委员会常务委员。获政府特殊津贴、中科院优秀导师奖、云南省三八红旗手称号和中科院首届妇女十杰提名奖。退休前连任中科院昆明动物研究所脑与行为研究组(神经精神药物药理学研究组)学术带头人、灵长类生物学研究室主任、本所学术委员会委员《动物学研究》副主编。曾任云南省动物学会副理事长、第六和第七届国家自然科学基金神经和心理学科二审评审组成员。

主持灵长类前额叶认知功能发育、衰老机制和相关脑功能疾病防治的研究工作,在研究所神经生物学学科的组建和发展方面做出了重要贡献。已发表论文近百篇,参与出版专著 3 部;主持获云南省自然科学成果一等奖 1 项,国家发明专利证书 3 项;合作获成果奖 8 项;与昆明植物所郝小江研究员合作主持的治疗老年痴呆症的Ⅰ类新药(西药)芬克罗酮(曾用名 KMBZ-009)2005 年被国家 FDA 批准进入临床试验。

在自创建的利血平化恒河猴模型上证实了去甲肾上腺素突触后 α_2、D_1 和 D_2 受体在工作记忆中起重要作用,相关论文发表后引用率一直居高。在Ⅰ类新药(西药)芬克罗酮研究中,带领学生通过大量实验证实芬克罗酮为部分钙激动剂,有保护神经元和增加神经递质释放的作用,从而可有效治疗老年性痴呆和老年性记忆障碍及其他相关疾病。